REMARKS

Amendment to the Specification

The specification has been amended to define a well known abbreviation used in the art, ME, at its first use as "myalgic encephalomyelitis". (See enclosed internet article entitled *Myalgic Encephalomyelitis).*

Amendments to the Claims

Claim 1 has been amended without prejudice and new claims 9 and 10 introduced to more clearly and distinctly point out the metes and bounds of preferred embodiments of applicants' invention. Support is provided in original claims 2-4 and in Examples 1 and 2 (page 9-18). Claims 2 - 4 are hereby canceled.

Information Disclosure Statement

At the time of writing, applicants' are not aware of any further references to draw to the attention of the Examiner. Those listed in the specification are given by way of background and can not be considered particularly pertinent.

Present Invention

The invention relates to a method of determining long-term psychological stress level in humans utilizing as a biological marker isoprostanes or their metabolites analyzed from body fluids such as urine by standard antibody assays. Applicants have surprisingly found that the level of this marker is significantly higher for individuals who exhibit high levels of psychological stress in a well established stress questionnaire based on "locus of control". Applicants

propose that their procedures could provide a reliable means of monitoring an individual's allostatic load to increase their awareness of exposure to long term psychological stress and thereby allow preventative steps to be taken.

Claims Rejection under 35 USC §112

In the Office Action mailed September 30, 2005 (hereinafter, "Office Action") claims 1-8 were rejected under 35 USC §112 first paragraph 3 (a) for lack of enablement. Applicants submit that the preferred embodiments recited in amended claim 1 and new claims 9 and 10 are fully enabled by the specification for the reasons set forth below.

The invention involves a method for determining psychological stress levels in humans. This is effected by measuring isoprostane levels in various bodily fluids. Such fluids are described on page 4, lines 18 – 21. Further, the measurement involves measuring isoprostane levels by detection of antibodies or antibody fragments. This is generally taught at page 4, lines 30 – 34. Commercially available test kits are already available to carry this out (see page 6, line 24 – page 7, line 2). A specific methodology for putting this into effect is described in detail in Example 1.

Claim 1 has been amended specifically to recite body fluid suitable for the measurement and also, the specific detection of antibodies or antibody fragments.

The Office Action also asserted that the specification does not clearly teach what is involved in psychological stress, how it is defined, and the threshold or normal values of psychological stress.

However, Example 2 clearly defines a protocol whereby stress level can be independently calibrated by means of a stress questionnaire followed by stress induction. The stress questionnaire is based on a "locus of control". It is also based on sound academic definition of psychological stress and its measurement, based on the work of Cohen et al J. Health and Soc. Behaviour 1983, **24**, pp. 386 – 396, as referenced on page 13, lines 23, 24. For example, Cohen in a chapter on *Stress and Illness* in Encyclopedia of Human Behavior (enclosed) defines stress as "the condition that results when person/environment transactions lead the individual to perceive a discrepancy between the demands of a situation and the persons resource". Thus, according to Cohen stress is the overall effect on the individual reacting to a host of stimuli.

The specification states on page 1, line 14, that psychological stress, also known as psycho-neuro-endodcrine stress, involves an assessment of the biological mechanisms underlying the psychological state. This focus on the physiological effect underlying the psychological state in the definition of psychological stress is entirely consistent with well established concepts in the art. For example Campbell's Psychiatric Dictionary states on page 628 (copy enclosed) that "Definitions of stress fall generally into two groups: those emphasizing the noxious or adverse nature of the stimulus originating in the environment (e.g., negative life events) and those emphasizing the subjects physiologic responses to the stimulus (in particular, the sympathetico-adrenal cortex system).

With this in mind, claim 1 has been amended to recite that the psychological stress level is measured from the measured isoprostane level by comparing the measured isoprostane level with isoprostane levels obtained from a control group assessed to have a low psychological stress. This is based on the aforementioned passage in Example 2.

Further, Claim 1 has also been amended to define the threshold psychological stress as a isoprostane level statistically higher compared with the average isoprostane level found in a low stress control group.

Based on the amended claims and above remarks, applicants submit that the specification adequately defines psychological stress, its measurement, the threshold and other criteria needed to carry out the invention without undue experimentation. All that is required for the person of ordinary skill in the art is to mimic the Examples, also bearing in mind the teachings of the aforementioned referenced academic article as well as others disclosed in the specification.

In the Office Action, claims 1 – 8 were also rejected under 35 USC §112 for omitting essential steps. Claim 1 has been amended and new claim 10 added that both include the steps of obtaining the sample, the nature of the sample, measuring the antibody or antibody fragments and performing the comparison.

Claim 2 (subject matter now incorporated in claim 1) was rejected as vague and indefinite because it is unclear what relationship exists between the isoprostanes and the antibodies. However, as stated, a specific methodology is given in the Examples, particularly Example 1.

Claim 3 (subject matter now incorporated in claim 1) was rejected as vague and indefinite because it was allegedly unclear how one can determine a psychological stress level in a human if the biological sample comprises more than one body fluid. Applicants' respectfully submit that a person of ordinary skill in the art would readily appreciate how to measure the antibody or antibody fragments in more than one fluid to obtain separate indications of psychological stress and to average them to enhance overall accuracy.

Claim 5 was rejected as vague and indefinite because it is unclear how psychological stress is associated with one or more conditions. It was remarked that it was unclear whether the applicant was merely stating that psychological stress is related to the recited disorders or whether one is trying to diagnose those disorders. Applicants' submit that from the tenor of the specification, it is merely the psychological stress level which is being measured and correlations between the psychological stress level and the condition being examined.

Claim 5 was rejected for use of the term "ME". This is a well-known abbreviation used in the art for a medical condition term and stands for "Myalgic Encaphalomyelitis" (see for example attached internet document). The specification has been amended to include the full term as suggested by the Examiner.

Applicants submit based on the above remarks that the amended claims particularly point out and distinctly claim the metes and bounds of applicant's invention.

Based on the amended claims and above remarks applicants respectfully request that the §112 rejections be reconsidered and withdrawn.

Claims Rejection under 35 USC §103

Claims 1 – 4, 7 and 8 were rejected under 35 USC 103(a) as being unpatentable over Morrow et al (US 5,891,622) in view of Moller et al (*Oxidative stress associated with exercise, psychological stress and life-style factors*, Chemico-Biological Interactions, 102 (1996) 17-36). Applicants respectfully submit that their amended claims are not anticipated by the combination of these references for the reasons set forth below.

Morrow et al is directed at method to analyze in vivo oxidative stress status in an organism by measuring glucuronidated form of isoprostanes isolated from the organism and determining a total isoprostane profile including the glucuronidated form.

Moller et al deals with oxidative stress and it association with factors such as exercise, psychological stress, and life style. The Office Action asserts that Moller et al discloses that psychological stress increases oxidative stress and that it would have been obvious to one of ordinary skill in the art to use the method of Morrow et al to also determine psychological stress because Moller et al teaches that psychological stress correlates to an increase in oxidative stress. The Office action further asserts that one of ordinary skill in the art would have had a reasonable expectation of success determining psychological stress using the methods of morrow et al because Moller et al shows that oxidative stress is correlated with psychological stress. Applicants' respectfully disagree with both assertions for the reasons set forth below.

In the second paragraph of Section 3.2 on page 24 of Moller et al state that "linkage of psychological stress to increased susceptibility to oxidative stress is rudimentary". Therefore, a person of ordinary skill in the art may have reasonably comprehended a "linkage" between psychological stress and susceptibility to oxidative stress from this reference but the person of ordinary skill could not deduce from this statement which causes the other (whether psychological stress causes oxidative stress, or *vice versa*). Moreover, the person of ordinary skill in the art could not have deduced that measuring oxidative stress would lead to a measurement (quantitative) of psychological stress and certainly not the measurement of an accumulated psychological stress level to which applicants' invention is directed, i.e., allostatic load.

Although a person of ordinary skill in the art might have seen a technique for measuring oxidative stress by isoprostane measurement from Morrow et al,

there can be no suggestion that the skilled person could be able to measure psychological stress directly by measuring isoprostanes. For example, Moller et al further state on page 24 that emotionally stressed rats have a higher content of 8-OHdG suggesting a direct connection, but this has not been studied in humans. Thus, without the benefit of hindsight, a person of ordinary skill in the art would not have had a reasonable expectation of success because the connection had never been tested in humans.

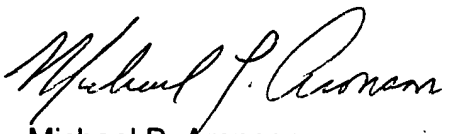
Finally, even in the unlikely event that a person of ordinary skill in the art had combined Morrow et al with Moller et al, applicants' claimed method would still not have resulted. There is no disclosure or suggestion in Morrow et al or in Moller et al that using antibody or antibody fragment assay in any of the stated body fluids could lead to an isoprostane assay which would thereby give a direct measurement of psychological stress level by comparing levels obtained in a test subject with corresponding levels in a low stress control group. Further, the use of the Percieved Stress Scale as a means of defining low stress control group and consequently a threshold psychological stress level is even more remote. All of these features are, of course, now embodied in claims 1 and 10.

Claim 5 was rejected under 35 USC 103(a) as unpatentable over Moller et al and Morrow et al in view of Cohen et al. However, this claim is dependent on claim 1 which is believed to meet all the requirements of patentability and therefore, it is submitted that no further comment is needed at this time.

Based on the above amendments and remarks, applicants respectfully request that the §103(a) rejections of claims 1 – 4, 7 and 8 over Morrow et al (US 5,891,622) in view of Moller et al (*Oxidative stress associated with exercise, psychological stress and life-style factors*, Chemico-Biological Interactions, 102 (1996) 17-36) be reconsidered and withdrawn and that the application be allowed to issue.

If a telephone conversation would be of assistance in advancing prosecution of the subject application, applicants' undersigned agent invites the Examiner to telephone him at the number provided.

Respectfully submitted,



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STRESS AND ILLNESS

Tracy B. Herbert and Sheldon Cohen
Carnegie Mellon University

Glossary

Adherence The degree to which patients follow the medical recommendations of practitioners.
Health behavior Activity undertaken by people who believe they are healthy in order to prevent future health problems.
Illness behavior Activity of people who feel ill with the purpose of determining the state of their health or finding a remedy.
Immune system The organs and structures that protect the body against harmful substances such as bacteria and viruses.
Neuroendocrine system An array of glands controlled by the nervous system that secrete hormones into the bloodstream.
Stress The condition that results when person/environment transactions lead the individual to perceive a discrepancy between the demands of a situation and the person's resources.
Sympathetic nervous system A division of the autonomic nervous system that enables the body to mobilize and expend energy during physical and emotional arousal.

THE RELATIONSHIP between stress and illness is the focus of a good deal of research performed in the field of health psychology. Health psychology is devoted to understanding the psychological factors associated with health and illness. One specific area of interest is determining the psychological factors related to the etiology of disease. Stress is one of the factors often studied that many people believe is related to health and disease. In fact, substantial evidence exists for associations between increased stress and reports of symptoms of disease as well as use of health services. Provocative evidence also exists for associations between increased stress and verified organic illness. In this chapter then, we will discuss stress, and specifically, focus on the mechanisms through which it might be possible for stress to influence health and illness.

I. DEFINING STRESS AND ILLNESS

A. What Is Stress?

Almost everyone has experienced the surge of adrenaline that comes with something sudden and unexpected, like when a speeding car almost hits us. One often hears people say they feel "stressed" because they are overworked, or they have "too much stress" in their lives. What is stress? Is it the adrenaline surge? The overwork? The way we feel emotionally? According to Lazarus and Folkman, two psychologists who have been important in developing a psychological theory of stress, stress is defined neither by an environmental event nor by a person's physiologic response to it. Rather, stress is defined by the person's *perception* of the environmental event. This perception involves the appraisal of potential harms, threats, and challenges posed by the event, as well as the individual's perceived ability to deal (or cope) with the harms, threats, and challenges. Thus, stress arises when a person appraises a situation as threatening or otherwise demanding, perceives that it is important to respond, and does not have an appropriate coping response immediately available. When individuals experience stress, or make a stress appraisal, they also characteristically experience negative emotions (e.g., anxiety, depression), changes in physiology, and changes in behavior patterns that increase risk for disease and mortality. [*See* STRESS.]

Encyclopedia of Human Behavior, Volume 4

Campbell's Psychiatric Dictionary

EIGHTH EDITION

ROBERT JEAN CAMPBELL, M.D.

OXFORD
UNIVERSITY PRESS
2004

to poorly established hemisphere dominance, so that visual impressions coming to both hemispheres are not clearly differentiated, and symmetrical engrams oriented in opposite directions are confused, as *b* and *d*, *p* and *q*. See *congenital aphasia; attention deficit hyperactivity disorder*.

stress Pressure; strain; a demand for response that threatens to exceed the resources of the subject. Definitions of stress fall generally into two groups: those emphasizing the noxious or aversive nature of the stimulus originating in the environment (e.g., negative life events) and those emphasizing the subject's physiologic responses to the stimulus (in particular, the sympathetico–adrenal medulla system and the pituitary–adrenal cortex system).

Although stimulus underload can constitute stress and trigger the same physiologic responses, stimulus overload is more commonly employed as the model of stress. Under conditions of stimulus overload, the ability to respond selectively to incoming information is impaired and the subject experiences feelings of excitement and tension. The sympathetico–adrenal medulla system (and secretion of the catecholamines epinephrine and norepinephrine) and the sympathetico–adrenal cortex system (and secretion of cortisol) are triggered. Thought processes tend to fragment, the subject is unable to integrate the signals received into a meaningful whole, judgment is impaired, and a sense of hopelessness and inability to cope mounts. See *general adaptation syndrome; holistic healing; post-traumatic stress disorder*.

stress disorder See *post-traumatic stress disorder*.

stress disorder, acute *Brief reactive dissociative disorder*; a condition that does not fully meet the criteria for *post-traumatic stress disorder* (q.v.) but is more severe than an adjustment disorder. The subject has been exposed to a traumatic event such as actual or threatened death or injury, and while witnessing or experiencing the event has felt intense fear, horror, or a sense of helplessness. At the same time, or immediately after, the subject experiences a number of symptoms: dissociative (e.g., stupor, depersonalization, detachment, amnesia), anxiety (e.g., hyperarousal, hypervigilance, intrusive recollections of the traumatic experience, sleep disturbances), anger, psychomotor agitation, despair, or social withdrawal. The episode lasts for less than 4 weeks, but the symptoms are severe enough to impair functioning and often prevent the person from obtaining appropriate medical or legal assistance or from telling family members about the experience.

stress interview A type of interview in which the patient is intentionally pressured, and the usual ways of reducing anxiety during the session are deliberately avoided. Such interviews may be useful in diagnosis, but their repeated use is generally contraindicated in the course of psychotherapy.

stressor, social See *life event*.

stretched speech Extension of the interval between successive acoustic stimuli. Dyslexic children typically are unable to recognize the very short–duration sounds of spoken speech, and they often have similar "fast element" recognition problems in other sensory modalities such as vision and touch. Language exercises that use stretched speech have often produced significant improvement in such children's ability to understand and respond to spoken language.

striatal cortical inputs Approximately 80% of all synapses in the striatum are cortical inputs, divided into

1. *motor*, which includes somatosensory, motor, and premotor cortices; in another system of nomenclature, the *matrix* compartment receives inputs most directly related to sensorimotor processing; and
2. *limbic associative*, which includes the amygdala, hippocampus and orbital, entorhinal, temporal, prefrontal, parietal, cingulate, and association cortex. In the second system of nomenclature, the *striosome* compartent receives inputs from neural structures affiliated with the limbic system.

At the striatal level a similar division occurs, with a motor putamen and a limbic caudate and ventral striatum (nucleus accumbens).

striatal dysfunctions These include Huntington disease (HD), Parkinson disease (PD), obsessive-compulsive disease (OCD), and Tourette syndrome (TS). See *striatum*.

OCD is characterized by intrusive cognitions, repetitive behaviors, and accompaniments of anxiety; although the cause and neuropathology of OCD are unknown, corticostriatal circuits involvng the caudate nucleus have been implicated. A diathesis for TS appears to be heritable and related to one subtype of OCD.

Like HD, PD is a degenerative disorder with well-established neuropathologic changes within the basal ganglia. The most consistent findings in HD and PD have been in the domains of *visuospatial ability, memory*, and *executive functioning* (qq.v.). Results of studies on HD, PD, OCD, and TS suggest the following neuropsychological profile in patients with corticostriatal dysfunction: impaired encoding and delayed free recall of information, with preserved storage demonstrated by correct recognition; deficits on certain procedural memory tasks, such as those measuring perceptual and motor skill acquisition; impaired visuomotor and visuoperceptual abilities; and disruption of subtle aspects of executive functions involving the appropriate maintenance and shifting of mental set. Deficits in executive functioning appear to be primary and have a secondary impact on the other domains.

striatal syndrome Disease of the striatum or striopallidal system, characterized, in general, by the following: (1) rigidity (a general increase of muscle tonus); (2) tremor (abnormal involuntary movements); (3) hypokinesia (poverty of voluntary, especially spontaneous movements); (4) impairment of associated movements; (5) absence of sensory disturbances; (6) absence of "true" paralysis, that is, absence of signs of involvement of pyramidal tracts.

striate cortex See *visual cortex, primary*

striatofugal projections The major output structure for the striatum is the *globus pallidus*. In both the *substantia nigra* and the globus pallidus, the relative segregation of limbic and sensorimotor inputs seen in the

psychohistory A general term for any literary work that attempts to understand historical events by providing a detailed psychological analysis of the characters involved. Psychohistory differs slightly from so-called PATHOBIOGRAPHY in that the latter almost invariably concentrates on psychoanalytic works while the former is eclectic. Also called *psychography*.

psychoimmunology PSYCHONEUROIMMUNOLOGY.

psychokinesis **1**. The hypothesized parapsychological phenomenon of an individual supposedly influencing a physical event without direct intervention. Also called *parakinesis*; abbrev., *PK*. **2**. Occasionally, in psychiatric writings, manic behaviour.

psycholagny Sexual excitement brought about by the use of one's imagination, usually by forming mental images.

psycholepsy A sudden loss of mental alertness, a feeling of hopelessness, helplessness, depression.

psycholinguistics A field that was created and named during an interdisciplinary conference held in the USA in 1953. Despite protestations from one of the prominent participants, Roger Brown, that the name sounded more like a description of a deranged polyglot than a scientific field, it has become an important part of psychology. Most broadly, the focus is upon the study of any and all behaviours that are linguistic. Subfields include the acquisition of language, bilingualism, pragmatics, speech-act theory, studies of grammar, the psychology of reading and the relationship between language and thought. Because of the ubiquity of verbal behaviour in humans, many psycholinguistic issues emerge in other areas as well, including cognitive psychology, memory, information processing, speech and hearing sciences, sociolinguistics, neuropsychology and clinical psychology. Compare with VERBAL LEARNING.

psycholinguistics, developmental A division of PSYCHOLINGUISTICS that focuses on the study of the acquisition of natural language by the child.

psychological **1**. Pertaining to psychology in any and/or all of its manifestations.

2. Characterizing an event, process, phenomenon or theory so as to emphasize its role in psychology as opposed to any other connotations which it may have, e.g. psychological test, psychological warfare. **3**. Pertaining to that which is mental in origin; see PSYCHOGENIC (1).

psychological anaphylaxis ANAPHYLAXIS, PSYCHOLOGICAL.

psychological autopsy AUTOPSY, PSYCHOLOGICAL.

psychological contract CONTRACT, PSYCHOLOGICAL.

psychological dependence DEPENDENCE, PSYCHOLOGICAL.

psychological distance DISTANCE, PSYCHOLOGICAL.

psychological environment Taken loosely, this term refers to all aspects of the environment that are psychologically relevant to an individual at any point in time. Exactly what constitutes this environment, however, is viewed very differently by different writers. For behaviourists it is characterized essentially in physical, objective terms; for Gestalt theorists it includes imaged, imagined and memorial aspects; for psychoanalytic thinkers it includes unconscious elements, motives, etc.

psychological factors affecting physical condition An unnecessarily long phrase put forward as a cover term for those mental factors that play a significant role in PSYCHOSOMATIC DISORDERS.

psychological freedom FREEDOM.

psychological me ME.

psychological moment MOMENT (1).

psychological present SPECIOUS PRESENT.

psychological reactance REACTANCE, PSYCHOLOGICAL.

psychological refractory period REFRACTORY PERIOD, PSYCHOLOGICAL.

psychological scale SCALE, PSYCHOLOGICAL.

psychological space LIFE SPACE.

psychological teratogen TERATOGEN.

psychological test A cover term for all tests of a psychological nature. See TEST and related entries for discussion and definitions of various kinds of test.

psychological time TIME, PSYCHOLOGICAL.

psychological type TYPE (esp. 3).

psychological warfare Originally, the use of psychological manipulations in the waging of wars. Most attempts are essentially morale-boosters for one's allies and -depressors for the enemy. More recently, use of the term has been extended beyond the military domain and is found in the context of similar morale-manipulating techniques used in marriages, business, sports, etc.

psychological weaning WEANING, PSYCHOLOGICAL.

psychologism Most commonly the point of view that psychology is *the* fundamental science and that the events of the world should be treated from that perspective. Precisely what shades of meaning the term conveys depends, of course, on who is using it. Many nonpsychologists use it as a form of reproach, psychologists typically don't.

psychologist Determining to just whom this term applies is no simple matter. The difficulties stem from the fact that some who claim it do so because they *practise* psychology, others because they *apply* it, others because they *teach* it and still others because they *research* it. When a formal definition is provided, it is usually done so to satisfy some particular practical and/or legal issue. For example, many governmental bodies that regulate licensing of psychologists require that an applicant have completed an advanced degree (a master's minimally, often a doctorate) at a recognized institution, undertaken one or more years of a supervised internship or practicum and passed a written examination. Criteria of this kind are most often applied when a psychologist is defined as one who is recognized or qualified to undertake any of a number of professional duties, e.g. a clinical psychologist, consulting psychologist, forensic psychologist or school psychologist. However, when assessing whether one who teaches and/or does research in psychology 'deserves' this four-syllable mantle, things become less clear. For example, the standard characterization of a

MYALGIC ENCEPHALOMYELITIS

Updated: Tuesday, October 5, 1999

Introduction

Recent discussions at the Brussels conference and elsewhere have helped to clarify that myalgic encephalomyelitis (M.E.) and CFS are not the same entity. There has been confusion about this, even in Britain where M.E. was first defined and studied under that name.

What exactly is M.E.? According to M.E. experts the key difference between M.E. and chronic fatigue syndrome is that M.E. requires the criterion of easy fatiguability following minimal exertion and a delay in recovery of muscle strength.

Definitions

M.E. has been described several times in medical literature. It was first defined in an editorial published in the Lancet in 1956 which discussed several epidemic outbreaks of prior years. This first description was rather loose and was not very specific. In later years Ramsay, EG Dowsett and others refined the definition of M.E. in various published papers.

After Ramsay died in 1990, Dowsett et al. wrote the latest version of the M.E. definition now known as the "London criteria". These have been used in recent papers by Costa (Brainstem perfusion is impaired in patients with CFS, QJM 1995; 88:767-773) and Scholey (A comparison of the cognitive deficits seen in M.E. to Alzheimer's Disease, Proceedings of the British Psychological Society, 1999, January, 12).